REMARKS

Claims 1-3 and 5-22 are pending in the present application and stand rejected under 35 U.S.C. §112, first and second paragraphs. Claims 8-10, 15-18 and 22 were subjected to restriction and are withdrawn from consideration.

Overview of the Amendments

Claim 1 has been amended to remove reference to the non-elected subject matter of neural progenitor cells. Claim 4 has cancelled as being redundant in view of the amendment of claim 1. Claims 8-10, 15-18 and 22 have been cancelled as drawn to a non-elected invention. Claims 5-7 have been amended to depend from claim 1 rather than newly cancelled claim 4. Claims 19-21 have beeb amended to recite that the cerebellar degeneration or central nervous system disorder is treated or prevented. Support for the foregoing amendments can be found throughout the specification.

The amendments to claims 1, 5-7 and 19-21, as well as the cancellation of claims 4, 8-10, 15-18 and 22, are without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record.

Claim Objections

The Examiner objects to claims 1-3 as encompassing non-elected subject matter. Claim 1 is amended to remove reference to neural progenitor cells. Applicants submit that the amendment fully addresses the Examiner's objections and request withdrawal of the objection.

35 U.S.C. §112, first paragraph

The Examiner rejects claims 1-5, 11 and 12, under 35 U.S.C. §112, first paragraph, as not providing enablement for *in vivo* applications of the method.

The Examiner justifies the rejection of these claims arguing that the "specification contemplates using the claimed method *in vivo* for gene therapy applications." These claims do not impose the limitation of therapeutic administration *in vivo*. The specification does indeed teach the use of this method for delivery of lentiviral particles to cells both *in vivo* and *in vitro*. However, "a positive limitation from the specification cannot be read into a claim that does not impose that limitation" (MPEP §2106). As explained in *In re Prater*, 415 F.2d 1393, 1404-1405 (CCPA 1969), "reading a claim in light of the specification, to thereby interpret that claim, is quite a different thing from 'reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that is was impermissible to import subject matter from the specification into the claims. In the present case, in making the rejection, the Examiner is impermissibly importing an *in vivo* therapeutic use limitation from the specification into the method of transducing claims where such a limitation is not recited.

Contrary to the Examiner's implication that the only asserted utility of the method for transducing cerebellar cells is *in vivo* gene therapy methods, the specification explains that the methods are useful for transducing cells *in vitro* as well as *in vivo*. See, e.g., page 39, lines 1-24 of the specification. Further, the specification, at page 5, line 24-25 explicitly states that the transduction methods "are useful for studying CNS and cerebellar disorders, and for testing therapies in representative animals." Thus the specification teaches utility of the method for both *in vivo* and *in vitro* transduction of cerebellar neurons.

Even if the Examiner's rejection were proper, Applicants submit that the specification fully enables use of the claimed methods for the purpose of *in vivo* gene therapy. A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). Only after the PTO

provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See *In re Bundy*, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981). The PTO has not met this initial burden.

The specification exemplifies *in vivo* administration of a lentiviral vector containing β-galactosidase as the protein of interest. The specification demonstrates that:

> A two microliter injection (10^4 – 10^5 infectious units) into a single lobule transduced up to 1500 Purkinje cells. With an estimated 20,000 Purkinje cells in all 10 lobules of the mouse cerebellum approximately 10% of all Purkinje cells and close to 100% of the injected lobule were transduced.

See the Specification at page 33, lines 8-12. The transduction of the Purkinje cells, which are cerebellar neurons, was detected based on expression and biological activity of the β-galactosidase protein. The specification provides an extensive list of genes encoding a wide variety of polypeptides, proteins or enzymes that, when expressed, one of skill in the art would expect to prevent or alleviate the effects of a particular cerebellar or CNS disorder (Specification at page 24, line 5 to page 25, line 2). In particular the specification suggests the expression of tyrosine hydroxylase to alleviate the symptoms of Parkinson's disease or the expression of MPIF-1, MIP-4 and M-CIF for treating multiple sclerosis.

The Examiner relies on a status report by an NIH ad hoc committee dated December 1995. This report is not considered by Applicants as relevant to the state of the art at the time the application was filed. In particular, the present application was filed on May 25, 2001 and claims priority of a provisional application filed May 26, 2000, which is five years after the release of this NIH report. The field of gene therapy has advanced a great deal over that period of time.

The Examiner argues that the greatest barrier to the success of gene therapy methods is targeting specific tissues. Applicants have demonstrated that the transduction methods of the present invention are capable of specifically transducing cerebellar neurons, such as Purkinje cells. Indeed, as noted above, the present method, with a single injection, transformed

approximately 10% of the Purkinje cells within a mouse brain and essentially 100% of the Purkinje cells that were resident in the lobule that received the injection. Thus, the present invention has overcome the barrier suggested by Miller et al. (1995), Crystal et al. (1995), and Deonarian et al (1998), in that the present invention teaches one of skill in the art how to transduce cerebellar neurons, such as Purkinje cells, in such a manner that the transduced cells express a protein of interest.

The Examiner relies on Verma et al. (1997) as teaching that "appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target." The present invention exemplifies the successful expression of a protein of interest in the desired transduced cells. Thus, the specification indeed teaches the use of regulatory elements effective in cerebellar neurons.

The Examiner also relies on Crystal et al. (1995) as demonstrating a need to increase the efficiency of gene transfer. As discussed above, the present invention achieved nearly 100% efficiency in transducing Purkinje cells *in vivo*. Essentially every Purkinje cell in the injected lobule was transduced by the lentiviral vector of the invention and expressed the protein of interest, β-galactosidase. Thus each of the technical barriers identified by the Examiner has been overcome by the present invention.

The Examiner further states:

> Beyond the technical barriers to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The claimed methods encompass use of vectors encoding a wide variety of therapeutic proteins and therefore are not limited to use in treatment of any particular condition and thus encompass use in treating any and all conditions that might be amenable to gene therapy.

Applicants submit that the claims are not drawn to treatment of **any and all** conditions. First, the claims are not drawn to gene therapy, but rather to transduction of cerebellar neurons. Second, even if the transduced cerebellar neurons were to be used in a gene therapy regimen, the conditions for which transduced cerebellar neurons might be appropriate falls well short of **any and all** conditions. As the specification states, appropriate uses would be for the treatment,

prevention or inhibition of diseases of the brain or other disorders of the central nervous system (see, e.g., page 5, lines 25-29).

Thus the present invention overcomes each of the technical barriers identified by the Examiner, *i.e.* difficulties in targeting vectors to desired cells, limited efficiency of transduction, and identifying appropriate promoter elements. In view of the fact that the present invention overcomes barriers that have hampered the success of gene therapy in the past, one of skill in the art would have no reason to doubt the ability of the present methods for transducing cerebellar neurons to have a therapeutic effect *in vivo*.

Further, Applicants adamantly disagree with the Examiner's implication that gene therapy cannot provide a therapeutic effect. Applicants call the Examiner's attention to Brooks, et al., "Functional correction of established central nervous system deficits with an animal model of lysosomal storage disease with feline immunodeficiency virus-based vectors," PNAS 99:6216-6221 (2002), which describes the use of lentiviral vectors to correct a central nervous system disorder. This study utilized β-glucuronidase-deficient mice, which have storage pathology in the eye and brain by several weeks after birth leading to progressive decline in retinal and neuronal function. By eight weeks of age, the mice are so debilitated that they cannot navigate the Morris water maze any long. See, Brooks et al. at page 6219, 2nd column. Four weeks after injection with the β-glucuronidase-lentiviral vector, the mice showed marked improvement in their ability to navigate a maze. The authors concluded:

> The combined results show that β-glucuronidase replacement ***reversed the severe neurological deficit*** in mice with established brain lysosomal storage disease.

Brooks et al. at page 6221, 2nd column (emphasis added). Thus the use of lentiviral vectors in gene therapy applications has been demonstrated to cause a therapeutic effect in a patient. Accordingly, Applicants submit that the present invention is fully enabled by the specification and request withdrawal of the rejection under 35 U.S.C. § 112.

Claims 6, 7, 13, 14, and 19-21 are also believed by the Applicants to be fully enabled. The Examiner also rejects claims 6, 7, 13, 14 and 19-21, under 35 U.S.C. §112, first paragraph,

stating that the specification fails to provide an enabling disclosure for therapeutic protocols. The specification exemplifies *in vivo* transduction of cerebellar cells. "To the best of the inventor's knowledge, this is the first report of direct gene transfer to cerebellar Purkinje cells." Specification at page 32, lines 13-14. Further, the specification teaches the expression of an exemplary gene of interest, β-galactosidase. The transduced cerebellar neurons expressing β-galactosidase was proportional to the number of neurons in the area exposed to the injected lentiviral vector. The specification describes, a number of proteins that one of skill in the art would expect to have a positive therapeutic effect on cerebellar degenerative diseases or central nervous system disorders. Any one of these therapeutic proteins could be substituted for β-galactosidase. Just as the β-galactosidase is expressed as a result of *in vivo* administration of the assay vector of Example 2, a lentiviral vector containing a gene encoding any of the numerous proteins described by the specification would result in a therapeutic effect to the vertebrate recipient. The Examiner has provided no reason why one of skill in the art would expect another protein to fail to be expressed from a similar lentiviral vector administered to cerebellar neurons in a similar manner. For these reasons, and for the reasons discussed above with regard to the rejection of claims 1-5, 11 and 12, Applicants submit that the specification fully enables therapeutic protocols as set out in claims 6, 7, 13, 14 and 19-21.

35 U.S.C. §112, second paragraph

The Examiner rejects claims 19-21 under 35 U.S.C. §112, second paragraph, as being indefinite in their recitation of "a method of treating or preventing" in the preamble because no treatment effect is achieved or required in the body of the claim. Claims 19-21 are amended to recite that the cerebellar degeneration or central nervous system disorder is treated or prevented. The scope of the claims is not altered by this amendment. Applicants submit that the amendment fully addresses the Examiner's concerns and request withdrawal of the rejection.

CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious over the art and comply with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

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